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Can the surface color of pharmaceutical tablets be used as a unique product identifier?

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ABSTRACT

There is an ongoing need for new or alternate approaches to distinguish between innovative pharmaceutical products from counterfeit or visually similar medicines. In this study we hypothesized that the quantitative measurement of the color on the surface of tablets, using the CIE $L^*a^*b^*$ color space, might be used to accomplish this objective. Several proof-of-concept studies were carried out in which ColorQuest XE colorimeter was used to measure the tristimulus L^*, a^*, and b^* color values from the surface of white and colored pharmaceutical tablets. Tristimulus values represent the red to green scale (a^*); the blue to yellow scale (b^*); and the lightness extreme (L^*). In a preliminary experiment, we demonstrated that each tablet from 54 products have a unique $L^*a^*b^*$ parameter within the 3D tristimulus color space. The utility of colorimetry in identifying imitator products was then demonstrated by comparing the color signatures of the innovator Viagra® tablets with imitator sildenafil tablets, which were procured from nine different online suppliers. While not an infallible technique, data in this study demonstrated that colorimetry might be used as a simple technique to identify innovative products and potentially alleviate the pandemic of counterfeit medicines, especially in areas around the world where counterfeiting is prevalent while sophisticated tools for their detection are not readily available.

1. Introduction

The distribution of counterfeit medicines and drug products is a major health concern, especially in developing countries with poor regulatory oversight [1]. Drug products that are identified as counterfeit are those that are ineffective, substandard, or illegal reproductions of innovator products. Counterfeiting therefore can apply to both branded and generic products and may include products with the correct ingredients, without active ingredients, with insufficient active ingredients, or with fake packaging and inadequate dosages [2].

To deter counterfeiting, drug products, and particularly tablets, have been manufactured with unique and identifiable codes and shapes. Serialization approach, for example, will be a requirement for all licensed product sold in the US from November 2017, and at the beginning of 2019 serialization will be a legal requirement in Europe for licensed drug products. In addition to deterring counterfeiting, this approach was devised to prevent reimbursement fraud and theft throughout the supply chain. The serialization approach however has created a real challenge for the pharmaceutical industry due to the complexity of performing serialization in multiple production lines in multiple locations [3]. Unfortunately, hallmarks or features are relatively easy to mimic. As a result, many of the pharmaceutical tablets cannot be readily distinguished from a genuine product by a casual observer or naked eye. Therefore, there is an ongoing effort to use alternative identification hallmarks that are difficult to emulate and/or to develop rapid and inexpensive techniques that can be operated by a layman person to identify products, and, if possible, to distinguish genuine products from counterfeit medicines.

In this study we present data that support the idea that quantitative measurement of the color on the surface of tablets with a colorimeter could be used as a unique product identifier. Colorimetry is simply “the measurement of color” by a

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colorimeter to identify an unknown color in reference to known colors [4]. Colorimeters measure the reflection or transmission properties of a subject as a function of wavelength that occupy the Z, X and Y planes in the CIE (international commission on illumination) three-dimensional uniform color space (Fig. 1). Three models, RGB (red, green, and black), CMYK (cyan, magneta, yellow, and key), and Lab, are commonly used to express color within the XYZ plane as a number. Lab color model is based on the opponent color theory [5], which states that, during visual perception, cone photoreceptors in the eye are linked together to form there opposing color pairs blue/yellow, red/green, and black/white [6]. When quantified by a colorimeter, these color pairs are expressed as tristimulus L^*, a^*, and b^* values, where a^* represents a value in the red to green scale, b^* represents a value in the blue to yellow scale, and L^* that measures lightness extremes, which ranges from a maximum value of 100 representing a perfect reflecting diffuser (white) and a minimum of zero representing black, a perfect absorber or non-reflecting object. The asterisks (*) in the Lab color space indicates that subsequent transformations of color data into coordinates are based on the mathematical models developed by CIE in 1976 as opposed to the models developed by Hunter in 1948. The only difference between the two is that CIE coordinates are calculated based on a cube root transformation of the color data, while the Hunter coordinates are based on a square root transformation of the data [6]. In the present study, Lab model was used to measure the tristimulus L^*, a^*, and b^* values. Using the Lab model is advantageous because it is device independence and includes all perceivable colors that approximate human vision. Therefore, its gamut exceeds those of the RGB model that has been used in several studies where color is constructed from the combination of the red, green and blue colors using a video spectral comparator (VSC) [7].

Historically, colorimetry has been used by the paint industry and to monitor the quality and stability of food and pharmaceutical products [8]. Colorimetry, for example, has been used to determine lycopene content and to establish a correlation between color and tomato quality and nutrition [9]. In more pertinent applications, several studies have demonstrated the utility of colorimetry in the pharmaceutical industry as a tool to monitor the quality of excipients and to measure the discoloration kinetics of tablets during stability testing [7,10–13].

Data presented in the present study suggests that the surface color of tablet as measured by a colorimeter may be used as unique product identifiers. The tristimulus $L^*a^*b^*$ color parameters of manufactured tablets measured prior to packaging could be recorded for each lot and used as a primary or supplementary identification codes to distinguish the product from counterfeit or generic tablet of visually similar shape and color. As highlighted in the subsequent sections, the authors recognize that colorimetry is not a fool proof technique, especially when one considers the effect of time, homogeneity and stability on color. These factors are important but are beyond the scope of this discussion. Furthermore, it should be recognized that colorimetry is a quantitative measure of the reflected spectrum and is not specific or selective for an analyte. Therefore, it should not substitute for chromatographic and spectroscopic techniques, such as nuclear magnetic resonance (NMR), Fourier transform infrared (FT-IR), near infrared (NIR), mass spectroscopy (MS), and Raman spectroscopy that have been developed to aid regulatory agencies in identifying authentic or counterfeit products chemically [14–16].

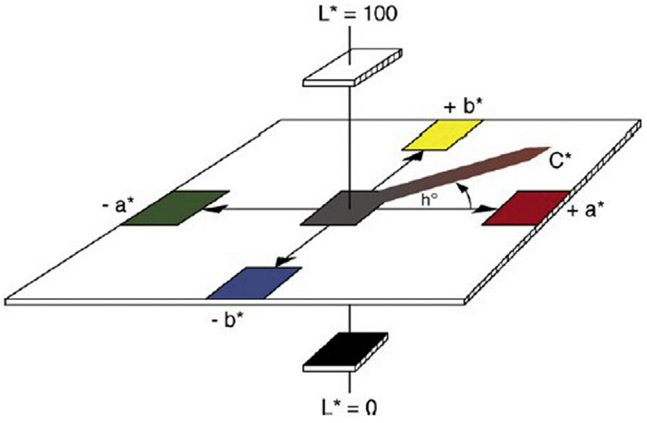

Fig. 1. CIE $L^*a^*b^*$ color space (courtesy of BYK Gardner, Columbia, MD).

2. Materials and methods

A HunterLab ColorQuest XE tristimulus colorimeter (Hunter Associates Laboratory Inc., Reston, VA) was used to measure the tristimulus L^*, a^*, and b^* values from the surface of tablet samples. Tablet samples were obtained from either commercial suppliers or purchased from online retailers as previously reported [17]. Measurement parameters were standardized to daylight illumination and 10-degree standard observer (D65/10). Spring loaded sample clamp was used to hold the specimen at the reflectance port with a 0.375-inch view area. A magnetic white ceramic disk on the face of the clamp ensured a consistent white background during measurements. One measurement from six tablets was performed to calculate the average and standard deviation of the L^*, a^*, and b^* values, which were then used to calculate chroma, color intensity, whiteness index, and total color difference based on the difference between the standard (D65/10) and sample's L^*, a^*, and b^* values [18].

Chroma (C^*_{ab}) measures the color degree of an area viewed to the brightness of an object and can be mathematically estimated from the following relationship:

$$C^*_{ab} = \sqrt{(a^{*2} + b^{*2})} \quad (1)$$

Color intensity (CI^*) measures the difference in location between a point and a central axis in the Lab color space [13]. CI^* can be calculated by:

$$CI^* = \sqrt{(100 - L^*)^2 + a^{*2} + b^{*2}} \quad (2)$$

Whiteness index (WI E313) measures the degree of departure of the object from a perfect white [19] and can be calculated as follows.

$$WI\ E313 = Y + 800(x_n - x) + 1700(y_n - y) \quad (3)$$

x and y are the chromaticity coordinates of the specimen where:

$$x = \frac{X}{X+Y+Z} \text{ and } y = \frac{Y}{x+y+z}$$

x_n and y_n are the chromaticity coordinates for the D65/10 standard, where $x_n = 0.3138$ and $y_n = 0.3310$.

Total color difference (ΔE^* or dE^*) between any two points in the color space, is estimated by applying the following relationship:

$$\Delta E^* = \sqrt{\Delta L^{*2} + \Delta a^{*2} + \Delta b^{*2}} \quad (4)$$